
Facial Soft-Tissue Fillers: Assessing the State of the Science conference—Proceedings report

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Summary: The American Academy of Dermatology and the American Society of Plastic Surgeons, with the support of other sister societies, conducted the Facial Soft-Tissue Fillers: Assessing the State of the Science conference in December of 2009. The American Academy of Dermatology and the American Society of Plastic Surgeons established a panel of leading experts in the field of soft-tissue fillers—from researchers to clinicians—and other stakeholders for the conference to examine and discuss issues of patient safety, efficacy, and effectiveness in relation to the approved and off-label use of soft-tissue fillers, and other factors, including the training and level of experience of individuals administering fillers. This report summarizes the deliberations and key points made by the panel and presenters to the panel, and includes a summary of the panel's near-term and longer term recommendations for next steps to help guide future efforts to address the safety, efficacy, and effectiveness of facial soft-tissue fillers. This report represents the panel's assessment of the medical knowledge available on facial soft-tissue fillers at the time of the conference. (*J Am Acad Dermatol* 2011;64:S53-65.)

The implantation of soft-tissue or dermal fillers for cosmetic procedures continues to be on the rise. In 2008, nearly 1.6 million procedures using soft-tissue fillers were performed in the United States, a 144 percent increase over the 650,000 performed in 2000.¹ More than two-thirds of these procedures used hyaluronic acid-based fillers,

making their use the third most performed cosmetic procedure in 2008.²

The steep increase in the use of these procedures is partly attributable to growth in the number of available products and options and increasing public interest in the procedure.³ Recognizing the growth in consumer demand for soft-tissue fillers, the U.S.

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Food and Drug Administration anticipates that submissions of premarket applications for these devices will continue not only for use in filling wrinkles (a U.S. Food and Drug Administration–approved use for available soft-tissue fillers) but also for new, currently off-label indications for soft-tissue fillers, such as augmenting and contouring of the face and body.⁴

In November of 2008, the U.S. Food and Drug Administration's General and Plastic Surgery Panel held a meeting to receive an "update on safety information collected on dermal fillers in the commercial setting, discuss current premarket and post-market approved study designs, and make recommendations on general issues concerning the study of various dermal fillers."⁵ A complete summary of this meeting is available.⁵ In response to the rapid growth in the use of soft-tissue fillers and the findings of the U.S. Food and Drug Administration panel, the following groups convened the Facial Soft-Tissue Fillers: State of the Science conference on December 6 through 7, 2009, in Washington, D.C.:

- American Academy of Dermatology (AAD) (sponsoring society)
- American Academy of Facial Plastic and Reconstructive Surgery (supporting society)
- American Academy of Ophthalmology (supporting society)
- American Academy of Otolaryngology—Head and Neck Surgery (supporting society)
- American Society for Aesthetic Plastic Surgeons (supporting society)
- American Society for Dermatologic Surgery (supporting society)
- American Society of Plastic Surgeons (ASPS) (sponsoring society)

A steering committee representing the ASPS, the AAD, and these supporting organizations was formed to help lead the effort, with co-chairs from the ASPS and the AAD. In addition to receiving support from these sponsoring organizations, the ASPS and the AAD received funding for the conference from several medical device companies involved in facial soft-tissue fillers (see the [Appendix](#) at the end of this article for a complete list). Throughout the process of developing the conference, the ASPS and the AAD received input from the U.S. Food and Drug Administration.

LITERATURE REVIEW

A literature review to identify and examine the available evidence on key issues raised by the U.S. Food and Drug Administration, and those identified

by the ASPS, the AAD, and the supporting medical specialty societies and organizations was conducted. In addition to presenting the current state of the evidence, the literature review highlighted gaps in the available evidence base.

Key questions

In creating a literature review search strategy, a set of key questions related to the state of the science pertaining to soft-tissue fillers was identified. The following 10 multipart questions ([Table I](#)) were developed based, in part, on the questions and issues discussed by the U.S. Food and Drug Administration General and Plastic Surgery Panel at their meeting in November of 2008. These questions were reviewed by members of the steering committee and revised based on their feedback.

Search strategy and design

A comprehensive search strategy was performed based on the key questions to search PubMed, which includes access to MEDLINE, and citations for selected articles in life science journals not included in MEDLINE. The search strategy was designed to ensure broad capture of all relevant articles. Search strings using MeSH (Medical Subject Headings, PubMed's controlled vocabulary for indexing studies) terms and key text terms were combined to produce the resulting search strategy:

- Varied constructs of search terms were captured with the use of truncation, as appropriate.
- Articles with abstracts in English.
- Articles focusing on humans.
- Studies published since January 1, 1994.
- Letters, editorials, and commentaries were excluded.

[Table II](#) lists the search terms and parameters that we applied. This search yielded a total of 621 abstracts.

A title and abstract review of these studies, applying inclusion/exclusion criteria developed in collaboration with the steering committee and based on study type and treatment type ([Table III](#)), was performed. The review of titles and abstracts yielded a total of 213 potentially relevant studies. Full-text articles for these studies were reviewed, and a precise classification of each article was performed. After the full-text review, a total of 198 unique, relevant studies were identified for inclusion in this review.

Based on the assumption that there was limited information on type and incidence of adverse events associated with use of soft-tissue fillers in general, case reports and case series, though methodologically limited for demonstrating cause and effect,

Table I. Key questions

1. What is the evidence for the short- and long-term safety, efficacy, and effectiveness of soft-tissue fillers for approved and off-label indications (where efficacy refers to the effects of the tissue filler under ideal conditions, and effectiveness refers to the effects under normal/routine or “real world” conditions)?
2. What is the evidence for the types and frequency of occurrence of adverse events associated with soft-tissue fillers for approved and off-label indications (e.g., use in the perioral area, including the lips, and volumization)?
3. What is the evidence for the delayed onset of adverse events (e.g., scarring and necrosis) following the administration of soft-tissue fillers for approved and off-label indications?
4. What is the evidence that the occurrence of adverse events varies by:
 - a. Type of soft-tissue filler?
 - b. Location of administration (e.g., for off-label use)?
 - c. Level of experience/training and supervision of staff administering soft-tissue filler (e.g., physician, nurse or other nonphysician)?
 - d. Clinical setting of administration?
5. What is the evidence that safety and efficacy data collected in premarket approval studies is consistent with and predictive of clinician experience with soft-tissue fillers in the postmarket setting?
6. What is the evidence that patients with Fitzpatrick skin types IV through VI who are administered soft-tissue fillers have outcomes similar to patients with Fitzpatrick skin types I through III who are administered soft-tissue fillers?
 - a. What is the evidence from comparative studies that these two subgroups respond with similar levels of safety and effectiveness to soft-tissue fillers?
7. What is the evidence that validated wrinkle severity and global aesthetic improvement scales are accurate and adequate for off-label indications (e.g., volume enhancement)?
8. What is the evidence for evaluation tools for predicting the efficacy/effectiveness and safety of soft-tissue fillers for wrinkles?
 - a. Is there evidence that these tools are accurate and adequate for predicting the efficacy/effectiveness (e.g., functional outcomes) and safety of soft-tissue fillers used for other uses (e.g., augmentation, volume enhancement)?
 - b. What is the evidence that certain evaluation tools are more predictive of efficacy/effectiveness and safety than others?
9. What is the evidence for the accuracy and adequacy of quantitative measures to evaluate the efficacy and safety of soft-tissue fillers?
10. What is the evidence for the accuracy of masked versus nonmasked evaluation, and live versus photographic evaluation of soft-tissue fillers?
 - a. What is the evidence that use of multiple observers is an effective evaluation tool?

were included as important sources of adverse event data, which is of high priority for evaluating soft-tissue fillers. See the companion Literature Review article for a complete description of the literature review process, data abstraction, and grading process used for this study.

OVERVIEW OF THE STATE-OF-THE-SCIENCE CONFERENCE

Key questions and topic areas addressed

Based in part on the literature review findings and the opinions and expertise of the conference panel, the ASPS and the AAD agreed to address the following issues.

Appropriate study design and need for more basic research

Panelists generally indicated that there is a need to look at and generate comparative evidence of the safety and effectiveness of soft-tissue fillers across the range of Fitzpatrick scores. The discussion focused on providing guidance to industry on appropriate study design, and included the following related issues for consideration:

- The distribution of Fitzpatrick scores in the population to determine what percentages would be representative of this distribution when recruiting for a study population.
- Appropriate study length of time for follow-up (e.g., by soft-tissue filler) or process for determining appropriate follow-up time, particularly given the increasing development and use of longer lasting products.
- Study of Fitzpatrick score subgroups as a requirement in the premarket approval or postmarket approval phase.
- Need for and feasibility of larger studies of soft-tissue fillers.
- Merits of histologic evaluation of soft-tissue fillers.
- Clinical endpoints for short- and long-term safety and efficacy/effectiveness that need to be studied (e.g., device migration, local tissue response, chronic inflammatory response, function, nerve sensitization) and how these differ by location of the soft-tissue filler.
- Consideration of appropriate control groups.
- Appropriate methods to collect low-incidence but possible severe adverse event information.

Update of labeling to reflect adverse events

The following issues emerged:

- How should an adverse event resulting from a soft-tissue filler be defined?

Table II. PubMed literature search strategy

Concept	Search String	Hits
General terms for dermal fillers	"dermal filler*" [tiab] OR "soft tissue filler*" [tiab] OR "soft-tissue filler*" [tiab] OR "injectable filler*" [tiab] OR "wrinkle filler*" [tiab] OR "skin filler*" [tiab] OR "facial filler*" [tiab] OR "collagen* filler*" OR (("cosmetic techniques" [MH] OR "rejuvenation" [MH]) AND ("collagen" [MH] OR "hyaluronic acid" [MH] OR "lactic acid" [MH] OR "durapatite" [MH] OR "polymethyl methacrylate" [MH] OR "silicone oils" [MH]))	OR AND 621
Collagen fillers	"cosmoderm" OR "cosmoplast" OR "cymetra" OR "fascian" OR "zyderm" OR "zyplast" OR "glutaraldehyde-cross-linked collagen" OR "evolence"	
Hyaluronic acid fillers	"juvederm" OR "perlane" OR "restylane" OR hylan-B gel [Substance Name] OR "hylaform" OR "puragen" OR "captique"	
Poly-L-lactic fillers	"sculptra" OR "new-fill" [Substance Name]	
Calcium hydroxylapatite fillers	"radiesse"	
Polymethylmethacrylate fillers	"artefill"	
Limits	(humans[MH] AND English[lang] NOT (editorial[pt] OR letter[pt] OR comment[pt]) NOT (review[pt] NOT (review[pt] AND (systematic[tiab] OR comprehensive[tiab] OR method*[tiab] OR medline*[tiab] OR pubmed*[tiab])))	

The asterisk (*) is a "truncation symbol" or "wildcard," which means that any characters that come after it are retrieved, including those with no other characters. The quotation marks (" ") mean that the search looked for the words as a phrase. The [tiab] means the search looked for the indicated term in the title or abstract. A search term with the [MH] after the term does not have the asterisk because it is a set MeSH thesaurus term and will not have any variations.

- Given the frequency with which soft-tissue fillers are administered for off-label uses, what is the appropriateness of including information about adverse events related to these off-label uses on the labeling of soft-tissue fillers?
- What should the level of U.S. Food and Drug Administration tolerance be for adverse events associated with soft-tissue fillers? Should it differ from the U.S. Food and Drug Administration's tolerance level for adverse events related to drugs?
- What should be the reporting process for adverse events? How is this reporting system affected by the level of U.S. Food and Drug Administration tolerance for adverse events associated with soft-tissue fillers? What other types of information should be reported?
- How should adverse events that may be related to interactions between different soft-tissue fillers be captured? How about potential adverse events related to repeated procedures in the same location?
- What should the threshold level be for adverse event reporting by industry?

Communicating adverse events to providers and consumers

Panelists indicated that labeling often does little to deter or control off-label use; nevertheless, information about potential adverse events needs to be communicated to providers and consumers. Representatives of the U.S. Food and Drug Administration

indicated that the pursuit of user-friendly information regarding these products should be a major focus, for both the health care provider and the consumer.

SUMMARY OF EVIDENCE AND CONFERENCE FINDINGS

Short- and long-term efficacy and effectiveness

Consensus findings and literature evidence results. All 198 studies identified in the literature review investigated and/or reported on the safety (e.g., occurrence of adverse events), efficacy, or effectiveness of soft-tissue fillers. Among these were 33 reports of randomized controlled trials. Hyaluronic acid fillers were most often investigated, whereas nasolabial folds were the most commonly injected area. Overall, the evidence indicates that soft-tissue fillers are effective and well tolerated for correcting nasolabial folds, other moderate to severe wrinkles and folds, and volume loss in cheeks. These findings were observed among patients seeking aesthetic facial rejuvenation and patients with human immunodeficiency virus-associated facial lipoatrophy. Specific findings pertaining to various facial soft-tissue fillers are summarized below. See the companion Literature Review article for additional discussion.

Hyaluronic acid. Although the expected duration of hyaluronic acid filler correction is 6 to 12 months, depending on the particular filler, 84 percent (36 of 43) of studies conducted follow-up evaluations of 3 months or longer.

Table III. Inclusion/exclusion criteria for abstract/title review

Included study types
Meta-analysis
Systematic review
Clinical trial
Randomized controlled trial
Randomized crossover trial
Controlled clinical trial
Uncontrolled clinical trial
Epidemiologic study
Cohort study
Case-control study
Cross-sectional study
Follow-up study
Evaluation study
Case report/series
Excluded study types*
Nonsystematic reviews
Guidelines
Included treatment types
Soft-tissue fillers, including the following:
Collagen
Hyaluronic acid
Poly-L-lactic acid
Calcium hydroxylapatite
Polymethylmethacrylate
Silicone oil fillers
Polyacrylamide gels
Excluded treatment types
Botulinum toxin
Polymers and collagen-related implants
Other dermal stimulators

*Particularly informative reviews and guidelines were retained to inform the background section.

Collagen. The expected duration of collagen filler correction is 3 to 4 months, and 94 percent of studies (16 of 17) conducted follow-up evaluations of 3 months or longer.

Calcium hydroxylapatite. Calcium hydroxylapatite was found to be superior to collagen (CosmoPlast; Inamed Corp., Santa Barbara, Calif.), and both fillers were found to have comparable safety and tolerability profiles. The two randomized controlled trials comparing calcium hydroxylapatite to hyaluronic acid fillers [Restylane (Q-Med Esthetics, Uppsala, Sweden) and Juvéderm (Allergan, Inc., Irvine, Calif.)] found calcium hydroxylapatite to be more effective in correcting nasolabial folds, whereas adverse event rates for both treatments were comparable. Although the expected duration of calcium hydroxylapatite filler correction is 1 year, 43 percent of studies (nine of 21) conducted follow-up evaluations of 1 year or longer.

Poly-L-lactic acid. Although the expected duration of poly-L-lactic acid filler correction is 2 years, 54 percent of studies (seven of 13) conducted follow-up evaluations of 2 years or longer.

Polymethylmethacrylate. Polymethylmethacrylate is the only U.S. Food and Drug Administration–approved filler with documented durability over a 5-year period.⁶

Key points

There are major gaps in the evidence base for the effectiveness of most injectable soft-tissue fillers for indications other than nasolabial folds. Furthermore, as most of the evidence is for the use of hyaluronic acid and collagen fillers, there is a lack of evidence related to the use of other important soft-tissue fillers. Another gap is evidence for effectiveness of various techniques; for example, injector techniques in the more carefully managed setting of clinical trials are likely to differ from those used in clinical practice (e.g., for facial contouring). As clinical practice evolves, the evidence needed to meet regulatory requirements is not necessarily the same as the evidence needed for market clearance and approval, further challenging the use of evidence-based medicine in this field.

Areas for improvement

Periodic evaluation of the evidence. The following recommendations are made:

- Establish the means to determine, on a periodic or ongoing basis, the current levels of evidence on efficacy and effectiveness.
- Determine the priority gaps in these bodies of evidence as they evolve with the introduction of new technology and indications.
- Develop a timeline and set of approaches with which to conduct this evidence review effectively.
- Where possible, distinguish the priority gaps in evidence for the respective purposes of regulatory requirements for market clearance/approval and informing clinical practice.

Develop a stronger evidence base. Encourage development of a stronger evidence base for currently recognized gaps, including the following:

- Soft-tissue filler classes other than hyaluronic acid and collagen.
- Important “off-label” indications (i.e., on- and off-face).
- Various injection techniques in all injection areas.
- The histology of degradation and product resorption.

Measures for soft-tissue efficacy and effectiveness

Consensus findings and literature evidence

results. Across the literature on soft-tissue fillers, effectiveness is often determined by the level of aesthetic improvement. Although aesthetic improvement may be subjective and difficult to quantify, a variety of evaluation tools have been developed to improve the validity and reliability of assessments. These tools include ratings of appearance, patient satisfaction, and treatment success, which were used in studies evaluating on-label or off-label uses of soft-tissue fillers. For studies on facial augmentation for human immunodeficiency virus–associated lipoatrophy, evaluation tools often included methods to determine skin thickness. Evaluation tools that were less frequently used included patient questionnaires on quality of life and psychological state, and three-dimensional imaging.

Ratings of appearance. Despite the large variation across the evidence with regard to soft-tissue filler type, injection technique, injection site, study population, and on-label versus off-label uses, the majority of studies evaluating aesthetic appearance included the use of a validated scale, such as the Global Aesthetic Improvement Scale, the Wrinkle Severity Rating Scale, the Facial Fold Assessment scale, the Lemperle Rating Scale, the Nasal Fold Severity scale, and the Modified Fitzpatrick Wrinkle Scale.

Ratings of treatment success. Several studies used scales to rate treatment success; however, none of these scales appeared to have been validated. Furthermore, these studies provided very little detail on how the scales were developed or what the criteria were for each score within the scale.

Measurements of skin thickness. Particularly in studies focusing on human immunodeficiency virus–associated lipoatrophy, skin thickness was a frequently assessed outcome measure. None of the methods for determining skin thickness was validated in these studies. The most frequently used method for measuring skin thickness involved skin calipers.

Although there are some validated scales that are available, training on the use of these scales and standardization across these validated scales is still needed. Based on an assessment of the available literature, the review concluded that there is a need for patient-reported outcome measures designed to measure satisfaction with facial appearance following aesthetic procedures.⁷

Research on patient-reported outcome measures to date includes creation of FACE-Q, a tool being developed and validated to measure clinically useful

patient-reported outcome measures of satisfaction and quality of life following elective surgical and nonsurgical facial rejuvenation. Sponsored in part by the ASPSP, the FACE-Q uses in-depth patient interviews to identify questions using specific language mirroring patient verbiage. It includes measures for specific areas of the face and has resulted in 36 different scales that can be used in combination to assess various patient-reported outcome measures.

Increasingly, patient-reported outcome measures are being used as primary endpoints. The U.S. Food and Drug Administration has indicated that it is receptive to patient-reported outcome measure research and has issued a guidance document on patient-reported outcome measure development. To demonstrate efficacy and effectiveness, however, clinically meaningful and scientifically rigorous patient-reported outcome measures are needed.

Key points

Soft-tissue filler injection relies on the subjective evaluation of aesthetic improvement to determine efficacy and effectiveness. As such, the lack of validation and standardization in accepted outcome measures (or scales or indexes) reduces the ability to generate rigorous evidence about the efficacy and effectiveness of soft-tissue fillers. Many of the current outcome measures have not been validated independently. The development of improved patient-reported outcome measures could strengthen clinical trials and generate evidence of greater relevance to clinicians and patients.

Areas for improvement

Develop and validate clinically meaningful outcome measures. These measures should incorporate psychometric variables, include three-dimensional aspects (e.g., using volumetric scales) of soft-tissue filler injection, and be based on techniques that are not limited to patient photography. The development and validation of patient-reported outcome measures should be encouraged as a primary method of assessing the efficacy and effectiveness of soft-tissue fillers in a clinically relevant way.

Adopt standardized validated outcome measures. Move toward scientifically based consensus regarding a small set of validated outcome measures for use in clinical trials and clinical practice in response to a need for more standardization across scales.

Short- and long-term safety

Consensus findings and literature evidence

results. There was great variation in the level of adverse event reporting across the studies reviewed from the literature. Most interventional and

epidemiologic studies (i.e., non—case series/reports) simply reported the incidence and severity of local and systematic adverse events.

Several studies reported safety data beyond adverse event incidence and descriptions of severity. A total of five studies found that the examined collagen filler had low potential for immunologic reactions. There remains a significant evidence gap for adverse events resulting from the use of soft-tissue fillers, including adverse events associated with the type of filler and technique used.

Key points

Major gaps in evidence related to soft-tissue fillers call for more organized and systematic collection of safety data. Increasing on-label use, expansion of off-label use, and varying injector technique are all major contributors to the need for improved safety data. Additional concerns about safety arise as more patients undergo multiple procedures involving the same or different fillers over time, often at different sites and performed by providers of varying expertise and experience. More research is needed on injection migration anatomy and related anatomical models. In looking to further this research, other clinical areas offer potential lessons in using best practices research and other systematic approaches to identifying and mitigating patient risk.

Areas for improvement

Patients undergoing procedures with multiple fillers. Establish data collection mechanisms to investigate risks to patients who undergo procedures involving the same or multiple fillers either simultaneously or over time.

Site preparation before filler use. Conduct research to determine whether site preparation before soft-tissue filler injection affects infection rates. Use the findings of this research to develop best practices or other protocols, as appropriate.

Data collection mechanisms. Establish data collection mechanisms to identify associations between various procedures/techniques and adverse outcomes. Establish data collection mechanisms to track/investigate the postinjection anatomical location of fillers.

Three-dimensional application of fillers. Develop a new anatomical atlas for use in research and clinical practice that incorporates current research and accounts for the three-dimensional application of fillers.

Adverse event reporting

Consensus findings and literature evidence results. A review of the literature identified 100

studies related to adverse event reporting. Of these studies, four provided analyses of individual databases, whereas the remaining 96 were case series or reports presenting a variety of adverse events. Additional presentations given at the state-of-the-science conference that reflected experience in practice reinforced the findings of the literature review.

Adverse event registries. Registries and databases have been used to collect adverse event data associated with injectable soft-tissue filler devices. Although it is difficult to use such data to demonstrate causal relationships between particular soft-tissue fillers and adverse events, they can help to identify possible associations. The largest adverse event registry identified by the literature review comprised a database maintained by Q-Med Esthetics (manufacturers of Restylane, Perlane, and Restylane Fine Lines). The database includes adverse event data from 1999 and 2000, which were collected from physicians in Europe, Canada, Australia, South America, and Asia. A retrospective review of these data found that approximately 144,000 patients were treated with hyaluronic acid in 1999. The study concluded that hypersensitivity was the greatest risk associated with hyaluronic acid fillers.⁸

- Manufacturer and User Facility Device Experience Database. The U.S. Food and Drug Administration maintains the Manufacturer and User Facility Device Experience database, which represents voluntary reports of adverse events involving medical devices, such as soft-tissue fillers. A recent U.S. Food and Drug Administration analysis of soft-tissue filler devices stated that 930 cases of adverse events were reported from January 1, 2003, through September 20, 2008. The most frequently reported injection site was the nasolabial fold, accounting for 35.6 percent of the reports in which the site of injection was specified. However, the majority of reported adverse events occurred in sites other than the nasolabial fold (e.g., lips, periorbital, perioral areas). Although the U.S. Food and Drug Administration's analysis provides some insights into adverse events associated with soft-tissue fillers, the U.S. Food and Drug Administration noted the limitations of the data analysis. There are significant limitations of the U.S. Food and Drug Administration's Adverse Event Reporting System, MedWatch, and the Manufacturer and User Facility Device Experience database. For example, although the Adverse Event Reporting System database is intended to encourage physicians to report any drug reaction, the report of the event

does not mean that the treatment caused the adverse event, just that the event occurred after treatment with the drug. In addition, although the aforementioned review was able to identify cases of adverse events in the Manufacturer and User Facility Device Experience database, the presenters experienced significant difficulty using the database interface, as there is only very limited terminology in the Manufacturer and User Facility Device Experience database related to soft-tissue fillers. There needs to be much more information in the database (including terminology about chemical classes of fillers, location of fillers, adverse events, method of treatment, and practitioner experience) for it to be a more informative tool for practice. The core specialty groups could collaborate with the U.S. Food and Drug Administration to clarify this terminology to ensure that it is consistent with practitioner terminology and relevant to current practice.

- **Injectable Filler Safety registry.** Another database identified in the literature and further described during the conference was the Berlin-based Injectable Filler Safety registry. The registry has become an important source of clinical information, as clinicians have contacted the registry to ask how to treat adverse events that occur in their patients.

Case series/reports. In addition to the three adverse event registries, our review identified 96 case series/reports presenting a variety of adverse events. [Table IV](#) presents a distribution of the case series/reports by the types of adverse events reported. The classification of adverse events is based on a 2008 U.S. Food and Drug Administration report on dermal filler devices. Among the various types of adverse reactions reported, swelling, inflammatory reaction, and erythema were most often reported.

Key points

Current adverse event reporting is voluntary and limited, in part because of concerns regarding liability, which varies across states, and related lack of information. These limitations in adverse event reporting diminish opportunities to improve practice. In addition, although the current U.S. Food and Drug Administration safety information and adverse event database for devices (Manufacturer and User Facility Device Experience) offers some useful information, its utility to clinicians, patients, and others interested in the safety of soft-tissue fillers is limited in several ways. Compared with other searchable databases, this database uses rudimentary search functions and ambiguous search terms. Furthermore,

Table IV. Distribution of case series/reports by adverse event type

Adverse Event	No. of Studies
Swelling	24
Inflammatory reaction	20
Erythema	18
Nonspecific mass	15
Beading	13
Blister/cyst	8
Pain	7
Allergic reaction	5
Infection	4
Vascular event	2
Migration	1
Other adverse event	14

the database search terms lack categories relevant to soft-tissue fillers.

Areas for improvement

Improve the facial soft-tissue filler adverse event reporting system. Collaboration with a number of national and international stakeholders may result in more effective and useful adverse event reporting. This initiative could involve working with the U.S. Food and Drug Administration to improve the Manufacturer and User Facility Device Experience database to incorporate improved search functions and terminology related to soft-tissue fillers. Injectors' profile information (e.g., professional status) and patient-reported outcome measures would also be useful to collect in this database. In addition or alternatively, the initiative could examine the Berlin registry as a model whose attributes could be adapted for use in the United States. Another potential model could involve establishing adverse reporting systems with patient safety organizations.

Clarify the legal implications and requirements for reporting adverse events. Currently, physicians may be hesitant to report adverse events because of potential exposure to legal actions. Furthermore, differences between and across states may lead to confusion in adverse event reporting requirements. It would benefit the validity of adverse event reporting and core cosmetic specialists to investigate and clarify the legal status and associated requirements of adverse event reporting for clinicians, including any important differences across states.

Training and education of practitioners administering soft-tissue fillers

Consensus findings and literature evidence results. None of the studies identified in the

literature review directly evaluated the level of experience or training of practitioners administering the filler. In most cases, studies did not indicate who provided the injections. Findings suggest risks involved with soft-tissue filler injections administered by unlicensed practitioners and the importance of public health officials' awareness of adverse events associated with such injections.⁹ In addition to injector training, technique may also have an effect on adverse events.

Key points

Given the evolving nature of soft-tissue fillers, expanding indications, and the variable practices associated with their use, there is considerable need for training and education to improve and ensure quality of care and patient outcomes. As many health care practices are regarded increasingly as commodities, the role of physicians could be diminished. Efforts must be made to counter unsafe trends and ensure that consumers are aware of the risk associated with using unqualified practitioners.

Areas for improvement

Develop evidence-based training and education programs. Core cosmetic medicine specialty and subspecialty societies should collaborate in developing and providing evidence-based training and education programs intended to improve quality of care and patient outcomes. These programs must distinguish between on-label and off-label uses as appropriate. The certification associated with such training and education will help patients to identify properly credentialed/qualified clinicians to perform soft-tissue filler procedures.

Develop a consumer awareness/information campaign. The core cosmetic medicine specialty and subspecialty societies should develop a consumer awareness/information campaign that conveys the importance of receiving soft-tissue filler procedures from properly credentialed/qualified clinician injectors. Information should pertain to the potential for adverse events and other risks associated with receiving injections from an uncertified injector.

Improved communication

Consensus findings and literature evidence results. Although our literature review did not evaluate communication challenges surrounding the state of the science of dermal fillers, for any of the aforementioned areas for improvement to occur, it will be necessary for the core specialty societies to increase communications with the U.S. Food and

Drug Administration and improve communications within and among their member organizations.

Key points

Consistent with prevailing regulations, industry is prohibited from sharing information about off-label use of soft-tissue filler materials. Furthermore, communications with the U.S. Food and Drug Administration are limited regarding evidence requirements for expanding approved indications for soft-tissue fillers. The development of soft-tissue fillers and clinical trials to establish their safety and efficacy/effectiveness would be improved by new guidance from the U.S. Food and Drug Administration on such aspects as appropriate trial design, patient selection, and outcome measures. Although communication has improved in recent years, better pretrial communication with the U.S. Food and Drug Administration would improve the efficiency and usefulness of clinical trials conducted for gaining market approval/clearance of soft-tissue fillers.

In addition to the need to further engage with the U.S. Food and Drug Administration, current communication levels and collaboration among core cosmetic medicine specialty and subspecialty societies need to keep pace with the evolving needs of stakeholders. This state-of-the-science conference was a step toward increasing communication and collaboration between the core cosmetic medicine specialty and subspecialty societies.

Areas for improvement

Establish a dialogue. The core specialty and subspecialty societies should establish a dialogue involving the U.S. Food and Drug Administration, clinicians, and industry to identify clinically relevant outcome measures and adverse events for soft-tissue fillers, which would inform the design of clinical trials, postmarketing surveillance, and other studies. This dialogue would address, for example, designing studies with appropriate duration for capturing outcomes and adverse events commensurate with various classes of soft-tissue fillers.

Engage in development of U.S. Food and Drug Administration guidance. The core specialty and subspecialty societies should involve industry in working closely with the U.S. Food and Drug Administration to develop current guidance for clinical trials and other data collection related to obtaining market approval/clearance for new indications, particularly beyond nasolabial folds. The core specialty and subspecialty societies should also work with and encourage the U.S. Food and Drug Administration to reduce the length of regulatory

review cycles, including U.S. Food and Drug Administration time and industry sponsor time, as appropriate, without diminishing the quality of the review process.

Establish an electronic mailing list. The core specialty and subspecialty societies should establish an electronic mailing list for the membership of the core cosmetic medicine specialty and subspecialty societies on the science, evidence base, and quality of care related to soft-tissue fillers.

Improve communication with patient advocacy groups. The core specialty and subspecialty societies should improve communication with patient advocacy groups whose missions may include matters related to cosmetic medicine, including for such purposes as developing and validating patient-reported outcome measures, sharing information about quality of care associated with soft-tissue fillers, and gaining patient/consumer input on these and related matters.

Develop a monitoring function. The core specialty and subspecialty societies should develop a monitoring function to capture relevant research findings, evidence reports/syntheses, updated evidence-based practice guidelines, and other information that may be shared with clinicians and other stakeholders in soft-tissue fillers.

Current and future research needs

Consensus findings and literature evidence results. The majority of studies identified in our literature review were case series or reports documenting the use of hyaluronic acid ($n = 39$). The most common study type identified in all soft-tissue filler studies was case series/case reports ($n = 97$). Although case reports and small case series are not typically included in an evidence review, we reviewed these study types for this report given our awareness that there is little information from available sources on adverse events associated with use of soft-tissue fillers. Case reports and case series, though methodologically limited for demonstrating causal relationships between interventions and outcomes, can be useful sources of adverse event data, especially where such data are scarce, as is the case for soft-tissue fillers. Furthermore, although the body of evidence we identified demonstrated that soft-tissue fillers are efficacious, effective, and in general fairly safe, the vast majority of studies we examined had short follow-up periods. Only one study followed patients for at least 5 years. Table V summarizes the distribution of the articles identified by study design and soft-tissue filler type.

Table V. Full-text studies by type of study and type of soft-tissue filler

Type of Study	Collagen	HA	PLLA	CaHA	PMMA	Other	Total*
SR	0	1	1	0	0	2	4
RCT	13	25	2	3	2	1	33
CCT	2	0	0	0	0	0	2
UCT	1	13	4	15	0	8	41
Cohort	1	4	7	2	1	4	18
Cross-sectional	0	1	0	1	0	1	3
Case series	17	39	19	11	10	20	97
Total	34	83	33	32	13	36	198

HA, Hyaluronic acid; PLLA, poly-L-lactic acid; CaHA, calcium hydroxylapatite; PMMA, polymethylmethacrylate; SR, systematic review; RCT, randomized controlled trial; CCT, controlled clinical trial; UCT, uncontrolled clinical trial.

*Citations pertaining to more than one soft-tissue filler type within a study are counted for soft-tissue filler, but only once for the "Totals" column.

Areas for improvement

Encourage and work with industry to design clinical trials. To develop a stronger evidence base that addresses evidence gaps previously mentioned, the core specialty and subspecialty societies should encourage and work with industry to design clinical trials that:

- Involve head-to-head comparisons of new and existing fillers using comparators representing standard care.
- Include standardized validated methods for assessing outcomes.
- Examine long-term safety and effectiveness.
- Incorporate clinically meaningful patient-reported outcome measures to the extent possible.
- Include evaluation of injection techniques (where such techniques may affect outcomes).
- Involve appropriately representative patient types (e.g., Fitzpatrick skin types IV through VI, sex, age).
- Provide for specific and detailed reporting of adverse events.

As discussed throughout the conference, there remains an unmet need for clinical trials that reflect current clinical practice. By encouraging research that incorporates these recommendations, the field will be much closer to addressing this need.

CONCLUSIONS

The Facial Soft-Tissue Fillers: Assessing the State of the Science conference, held December 6 through 7, 2009, represents the first multistakeholder conference focused on soft-tissue fillers. The key findings and recommended areas for improvement that emerged from the conference are an important initial

step toward addressing concerns over the safety, efficacy, and effectiveness of facial soft-tissue fillers.

Amid this growing demand for facial soft-tissue fillers are major gaps in the evidence base for the effectiveness of most injectable soft-tissue fillers for indications other than nasolabial folds. The majority of the current evidence base pertains to the use of hyaluronic acid and collagen fillers, with little devoted to the use of other important soft-tissue filler classes. To generate rigorous evidence about the efficacy and effectiveness across soft-tissue fillers, off-label indications, and varying injection techniques, it is imperative that validated and standardized outcome measures are established. As they are in other areas of health care, patient-reported outcome measures must play a greater role in the evaluation of soft-tissue filler injection. Demonstrating an improvement in patient-reported outcome measures, for example, can strengthen the validity and relevance of clinical trial findings for physicians and patients.

Major gaps in the soft-tissue filler evidence base can also be addressed, with increased efforts for organized and systematic collection of safety data. As more patients undergo multiple procedures and the applications of fillers continue to expand, more research is needed to understand, for example, injection migration and related anatomical models. Another important component of safety is adverse event reporting in the various at-risk patient populations. Currently, adverse event reporting is voluntary and limited, and improving this data collection and reporting capacity is needed to provide ongoing monitoring and feedback toward improving soft-tissue filler technology, clinical practice, and quality standards.

The rapidly expanding use of and indications for soft-tissue fillers necessitates commensurate development of training and education programs to improve the quality of care and patient outcomes. Furthermore, it is critical that consumers are aware of the risks associated with using unqualified practitioners and of other risks that may arise associated with these procedures. Finally, an increase in the level

and types of communication involving U.S. Food and Drug Administration, industry stakeholders, and clinical investigators will improve the efficiency and usefulness of clinical trials conducted to gain market approval for facial soft-tissue filler products.

The ASPS and the AAD contracted with The Lewin Group, a health and human services consulting firm located in the Washington, D.C., metropolitan area, to provide analytical support to the conference, including a systematic literature review to inform the work of an expert panel that was to be established for the conference. The Lewin Group was also contracted to facilitate the expert panel discussion during the conference and summarize the findings of the conference in the present report.

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APPENDIX

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